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# Influence of Liquid and Vapourized Solvents on Explosibility of Pharmaceutical Excipient Dusts

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**Keywords:** dust explosion, hybrid mixture, solvent admixture, pre-wetting, excipient dust, MCC, microcrystalline cellulose, lactose, explosion severity, explosion likelihood

## Abstract

Hybrid mixtures of a combustible dust and flammable gas are found in many industrial processes. Such fuel systems are often encountered in the pharmaceutical industry when excipient (non-active ingredient) powders undergo transfer in either a dry or solvent pre-wetted state into an environment possibly containing a flammable gas.

The research described in this paper simulated the conditions of the above scenarios with microcrystalline cellulose (MCC) and lactose as excipients, and methanol, ethanol and isopropanol as solvents. Standardized dust explosibility test equipment (Siwek 20-L explosion chamber, MIKE 3 apparatus and BAM oven) and ASTM test protocols were used to determine the following explosibility parameters: maximum explosion pressure ( $P_{max}$ ), size-normalized maximum rate of pressure rise ( $K_{St}$ ), minimum explosible concentration (MEC), minimum ignition energy (MIE), and minimum ignition temperature (MIT).

Because the MIKE 3 apparatus and BAM oven are not closed systems, only baseline excipient-alone testing and excipient pre-wetted with solvent testing were possible for MIE and MIT determination. With the Siwek 20-L chamber (a closed system), it was feasible to conduct  $P_{max}$ ,  $K_{St}$  and MEC testing for all three cases of the dust alone, pre-wetted with solvent, and with solvent admixed to the combustion atmosphere at 80 % of the lower flammability limit for each solvent prior to dust dispersal.

The experimental results demonstrate the significant enhancements in explosion likelihood and explosion severity brought about by solvent admixture in either mode. The extent of solvent influence was found to be specific to the given excipient and method of solvent addition. Solvent burning velocity considerations help to account for some of the experimental observations but for others, a more rigorous evaluation of solvent and excipient physical property data is needed.

## 1. INTRODUCTION

Hybrid mixtures consist of a flammable gas and a combustible dust, each of which may be present in an amount less than its lower flammable limit (LFL)/minimum explosible concentration (MEC), and still give rise to an explosible mixture [1]. The focus here is often on admixture of a flammable gas in concentrations below the LFL of the gas itself to an already explosible concentration of dust [1]. As described by Amyotte et al. [2], hybrid mixture research is typically conducted with three possible approaches: (i) gaseous solvent at room temperature existing in the combustion atmosphere prior to dust dispersal, (ii) liquid solvent at room temperature requiring flashing-off for admixture to the combustion atmosphere prior to dust dispersal, and (iii) liquid solvent at room temperature admixed as a liquid with the dust prior to dust dispersal.

Amyotte and Eckhoff [1] note that the influence of the co-presence of a flammable gas on the explosibility parameters of a fuel dust alone is well-established. These effects include higher values of explosion overpressure and rate of pressure rise, and lower values of minimum explosible concentration and minimum ignition energy [1]. There remains, however, a need for continued research on hybrid mixtures [3] given the range and diversity of industrial applications that can give rise to hybrid fuel systems as seen in recent studies [4-11].

The scope of the current work is the prevention and mitigation of explosions of hybrid mixtures consisting of a combustible dust and a flammable gas, or a combustible dust pre-wetted with a flammable solvent (i.e., the latter two scenarios described in the first paragraph above). This research is motivated by the occurrence of these scenarios in the pharmaceutical industry during transfer of dry or solvent-laden powders into a process unit that may contain a flammable gas [12]. The objective is the provision of explosion likelihood and explosion severity data acquired through best-practice testing methodologies using standardized apparatus. The specific hybrid fuel systems were selected to be representative of common pharmaceutical excipients (non-active ingredients) and solvents; the testing thus involved lactose and microcrystalline cellulose (MCC) dusts admixed with methanol (methyl alcohol), ethanol (ethyl alcohol) and isopropanol (isopropyl alcohol) solvents.

## 2. MATERIALS, APPARATUS AND PROCEDURES

All materials tested were pharmaceutical-grade in terms of composition and, in the case of the solids, particle size distribution (PSD) as-received from the suppliers. Tables 1 and 2 summarize the relevant material characteristics of the dusts (excipients) and solvents, respectively. Sieve analysis was used for the lactose PSD determination because of initial concerns about lactose solubility with Malvern light scattering analysis (which was performed for the MCC). The PSD results are consistent with the trend of the nominal mean diameters of 50  $\mu\text{m}$  and 75  $\mu\text{m}$  provided by the suppliers of the MCC and lactose samples, respectively.

Figures 1 and 2 show scanning electron micrographs (SEMs) of the MCC and lactose samples, respectively. MCC is observed to be fibrous or flocculent in nature, while lactose consists of irregularly-shaped, oblong particles.

**Table 1** Material characterization of excipient powders.

Characteristic	MCC	Lactose
Supplier	Sigma-Aldrich	Hilmar Ingredients
Particle Size [weight %]	Malvern Analysis: 90 % < 56 $\mu\text{m}$ 50 % < 27 $\mu\text{m}$ 10 % < 9 $\mu\text{m}$	Sieve Analysis: 98 % < 250 $\mu\text{m}$ 84 % < 150 $\mu\text{m}$ 62 % < 89 $\mu\text{m}$ 18 % < 75 $\mu\text{m}$
Moisture Content [weight %]	4.5	5.1

**Table 2** Material characterization of solvents.

Characteristic	Methanol	Ethanol	Isopropanol
Formula <sup>a</sup>	CH <sub>3</sub> OH	C <sub>2</sub> H <sub>5</sub> OH	C <sub>3</sub> H <sub>7</sub> OH
Molecular weight <sup>a</sup>	32	46	60
Lower flammability limit [volume %] <sup>b</sup>	6.7	3.3	2.2
Laminar burning velocity [cm/s] (Methanol, <sup>c</sup> Ethanol, <sup>d</sup> Isopropanol <sup>c</sup> )	56	42	41
Vapour pressure at 25 °C [mm Hg] <sup>a</sup>	127	59	43
Specific heat capacity (liquid) at 25 °C [J/mol·K] <sup>c</sup>	81	112	155
Boiling point at 1 atm [°C] <sup>a</sup>	64.7	78.5	82.2
Heat of vapourization at boiling point and 1 atm [kJ/mol] (Methanol, <sup>a</sup> Ethanol, <sup>a</sup> Isopropanol <sup>c</sup> )	35.2	38.5	39.9
Heat of combustion (liquid) at 25 °C and 1 atm with H <sub>2</sub> O(l) product [kJ/mol] <sup>a</sup>	-726.6	-1366.9	-1986.6
Specific gravity [20°C/4°C] <sup>a</sup>	0.792	0.789	0.785

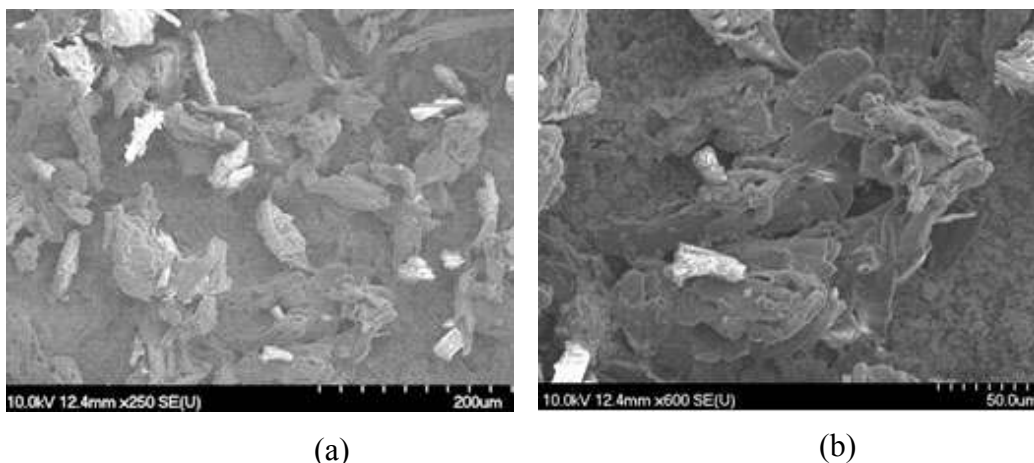
<sup>a</sup>Felder, R.M. and Rousseau, R.W., "Elementary Principles of Chemical Processes (3<sup>rd</sup> edition)", John Wiley & Sons, Inc., Hoboken, NJ (2005).

<sup>b</sup>Kuchta, J.M., "Investigation of Fire and Explosion Accidents in the Chemical, Mining, and Fuel-Related Industries: A Manual (Appendix A)", Bureau of Mines, US Department of the Interior, Avondale, MD (1985).

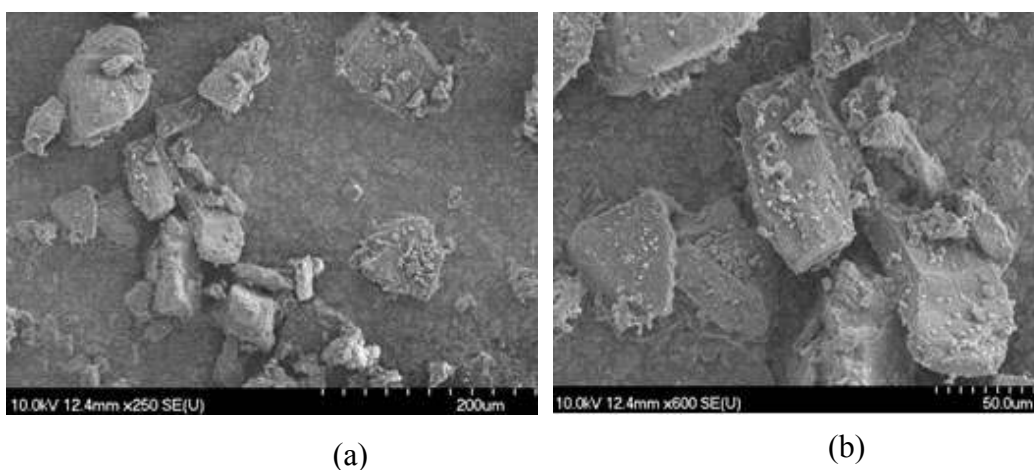
<sup>c</sup>NFPA, "NFPA 68: Standard on Explosion Protection by Deflagration Venting", National Fire Protection Association, Quincy, MA (2007).

<sup>d</sup>Lipzig, J.P.J., Nilsson, E.J.K., Goey, L.P.H. and Konnov, A.A., "Laminar Burning Velocities of n-Heptane, Iso-octane, Ethanol and their Binary Mixtures, Fuel, **90**, 2773-2781 (2011).

<sup>e</sup>Murphy, R.M., "Introduction to Chemical Processes. Principles, Analysis, Synthesis", McGraw-Hill, New York, NY (2007).



**Figure 1** Scanning electron micrograph of MCC powder: (a) 250 magnification, (b) 600 magnification.



**Figure 2** Scanning electron micrograph of lactose powder: (a) 250 magnification, (b) 600 magnification.

Explosibility parameters investigated include maximum explosion pressure ( $P_{max}$ ), size-normalized maximum rate of pressure rise ( $K_{St}$ ), minimum explosible concentration (MEC), minimum ignition energy (MIE), and minimum ignition temperature (MIT). ASTM (American Society for Testing and Materials) protocols [13-16] were followed using standardized dust explosibility test equipment: (i) Siwek 20-L explosion chamber for  $P_{max}$ ,  $K_{St}$  and MEC, (ii) MIKE 3 apparatus for MIE, and (iii) BAM oven for MIT. Apparatus and procedural descriptions can be found on the equipment manufacturer's web site ([www.kuhner.com](http://www.kuhner.com)) [2].

All hybrid mixture testing involved a fixed solvent concentration of 80 % of the respective lower flammability limit (Table 2), calculated according to the volume of the particular test apparatus. For the pre-wetted (PW) tests, the required amount of liquid solvent – methanol (M), ethanol (E) or isopropanol (IPA) – was mixed with the amount of dust corresponding to the dust concentration being tested. The pre-wetted dust was then dispersed into the specific apparatus (Siwek 20-L chamber, MIKE 3 apparatus or

BAM oven) via the usual procedure. For the atmospheric (ATM) tests (Siwek 20-L chamber only), the chamber was first evacuated to a pressure of 185 mm Hg (i.e., as close as possible to the respective solvent vapour pressures given in Table 2). The required amount of liquid solvent was then injected through a septum into the 20-L chamber, with the majority of the solvent flashing to vapour. The chamber was subsequently backfilled with air to a pre-dispersion pressure such that the chamber pressure at the time of dust ignition was approximately 1 bar. From a material balance perspective, any small amount of remaining liquid solvent would be vapourized by the shower of sparks originating from the chemical ignitors acting as the ignition source in the 20-L chamber [6].

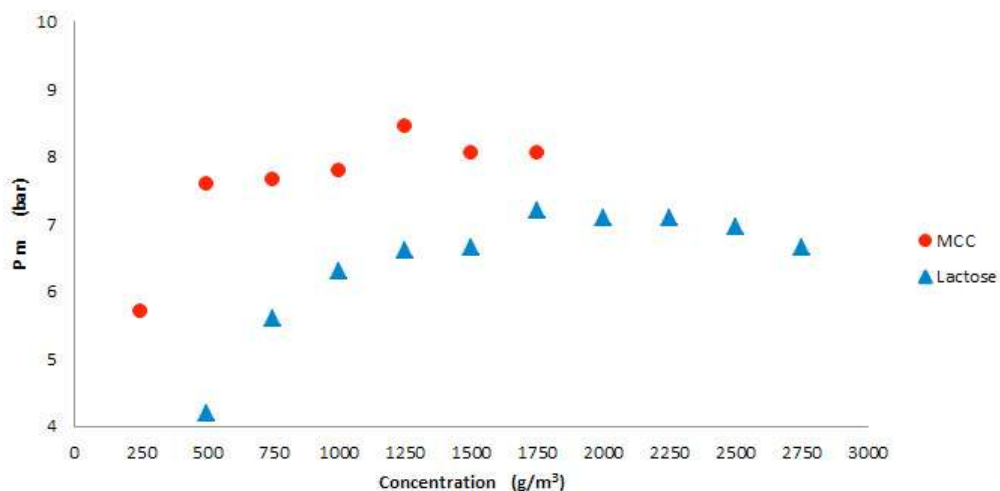
### 3. RESULTS AND DISCUSSION

In this section we present the experimental results according to severity of explosion consequences (overpressure and rate of pressure rise) and likelihood of explosion occurrence (minimum explosible concentration, ignition energy and ignition temperature). Preliminary data analysis drawing on Amyotte et al. [2] is presented, with further data interpretation ongoing.

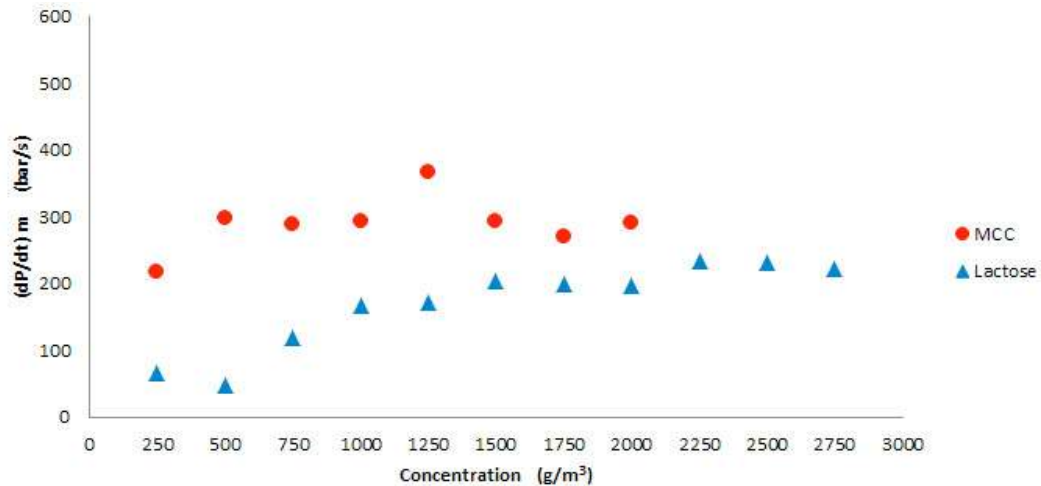
#### 3.1 Explosion Severity

Figures 3 and 4 show the influence of dust concentration on explosion overpressure,  $P_m$ , and rate of pressure rise,  $(dP/dt)_m$ , for the excipient dusts by themselves. (All figures in this section give average values of  $P_m$  and  $(dP/dt)_m$  at dust concentrations for which replicate testing was performed according to ASTM E-1226-10 [13].)

The data in Figures 3 and 4 display the expected trend of an increase in the measured explosibility parameter as dust concentration increases. Eventually, peak values of  $P_m$  and  $(dP/dt)_m$  are attained, followed by a parameter decrease or leveling-off with further increases in dust concentration. The higher peak values and lower optimum concentrations for MCC over lactose are indicative of both compositional differences between the two materials and the smaller particle size of the MCC (Table 1).



**Figure 3** Influence of dust concentration on explosion overpressure of MCC and lactose (baseline excipient alone).



**Figure 4** Influence of dust concentration on rate of pressure rise of MCC and lactose (baseline excipient alone).

Tables 3 and 4 give the complete  $P_{\max}$  and  $K_{St}$  data sets for all test conditions.

**Table 3**  $P_{\max}$  and  $K_{St}$  data for MCC.

Material	$P_{\max}$ [bar(g)]	$K_{St}$ [bar·m/s]
MCC	8.5	103
MCC + M (PW)	7.9	144
MCC + E (PW)	7.8	117
MCC + IPA (PW)	7.7	116
MCC + M (ATM)	7.9	168
MCC + E (ATM)	8.3	149
MCC + IPA (ATM)	8.4	172

**Table 4**  $P_{\max}$  and  $K_{St}$  data for lactose.

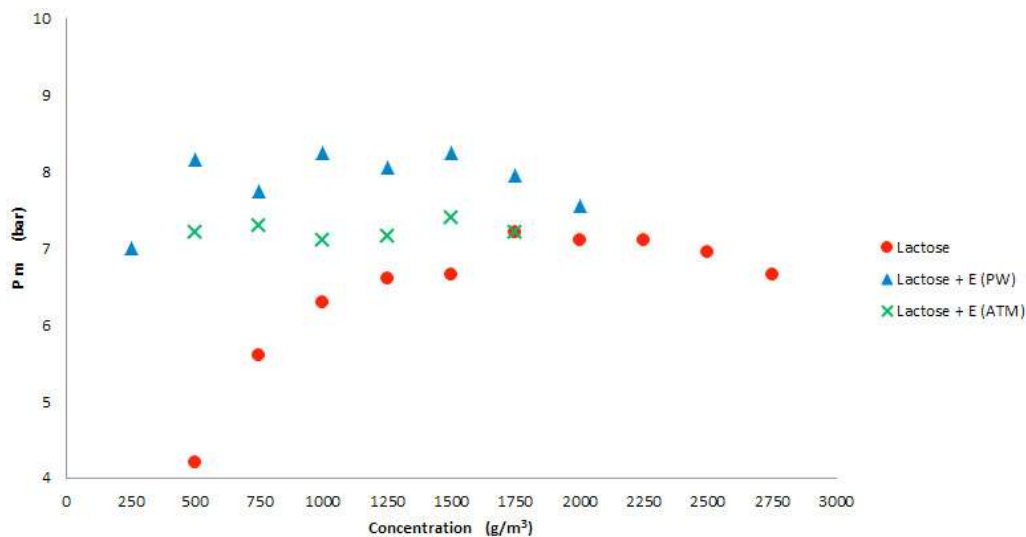
Material	$P_{\max}$ [bar(g)]	$K_{St}$ [bar·m/s]
Lactose	7.1	65
Lactose + M (PW)	8.1	149
Lactose + E (PW)	8.4	148
Lactose + IPA (PW)	8.6	144
Lactose + M (ATM)	8.0	155
Lactose + E (ATM)	7.4	94
Lactose + IPA (ATM)	7.8	102

As preliminary commentary [2], we offer the following thoughts on the trends displayed by the data in Tables 3 and 4. In all cases, pre-wetting (PW) of MCC and lactose with solvent had a measurable impact on both  $P_{max}$  and  $K_{St}$ . As expected, the influence was generally an enhancement of each explosibility parameter; the lone exception was  $P_{max}$  for MCC which displayed a decrease of 0.6-0.8 bar(g) with solvent admixture by pre-wetting.

While the magnitude of the effect on  $K_{St}$  of solvent pre-wetting for MCC was generally distinguishable for the different solvents, this was not the case for lactose. Pre-wetting of lactose with each of the three solvents resulted in similar  $K_{St}$  values. This suggests an approximate correlation of  $K_{St}$  with burning velocity (Table 2) for pre-wetted MCC but not for pre-wetted lactose. Such a correlation was previously shown to hold in the atmospheric-type tests conducted by Amyotte et al. [6] for polyethylene admixed with various hydrocarbons.

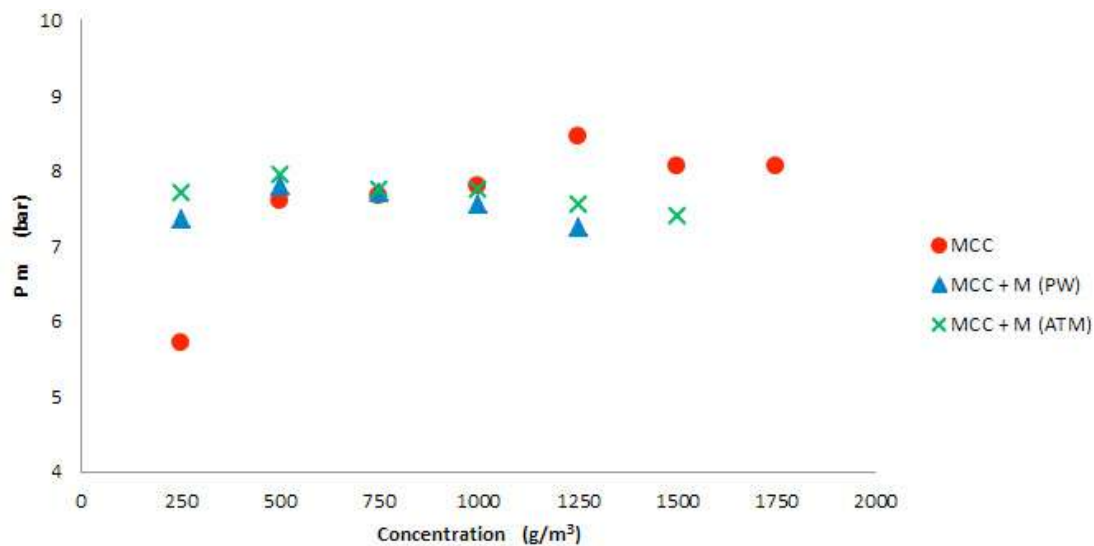
The atmospheric (ATM) test data in Tables 3 and 4 show a reversal of the above trend for the two excipients. Here, the admixed solvent has generally the same effect on  $K_{St}$  of MCC regardless of the nature of the solvent. On the other hand, the lactose  $K_{St}$  values can be approximately ranked according to solvent burning velocity.

These observations are somewhat speculative, and it is likely that some of the other solvent physical properties shown in Table 3 (and perhaps others related to solubility) will be required to advance the phenomenological modeling of these data. What seems clear at present is that the influence of each solvent is specific to the particular excipient and the method of admixture (pre-wetting or atmospheric). This is clearly demonstrated by Figures 5 and 6 which display overpressure data for the lactose/ethanol and MCC/methanol systems, respectively.



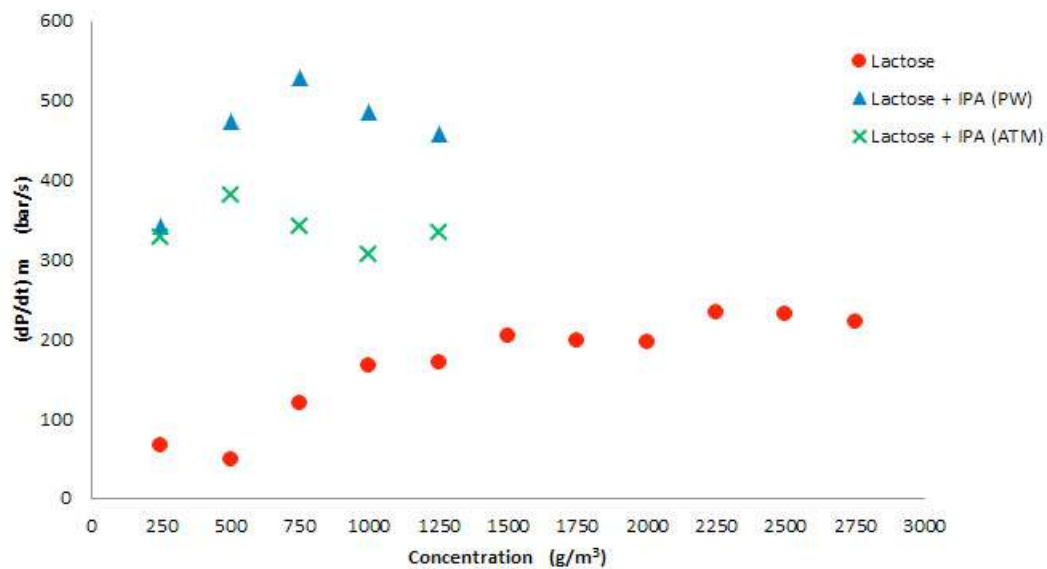
**Figure 5** Influence of ethanol admixture on explosion overpressure of lactose.



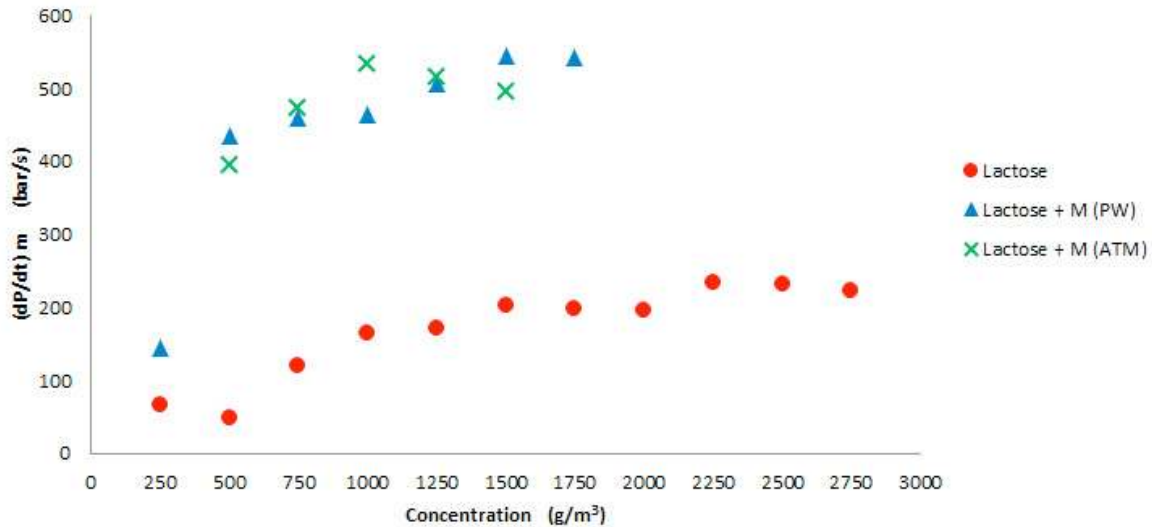


**Figure 6** Influence of methanol admixture on explosion overpressure of MCC.

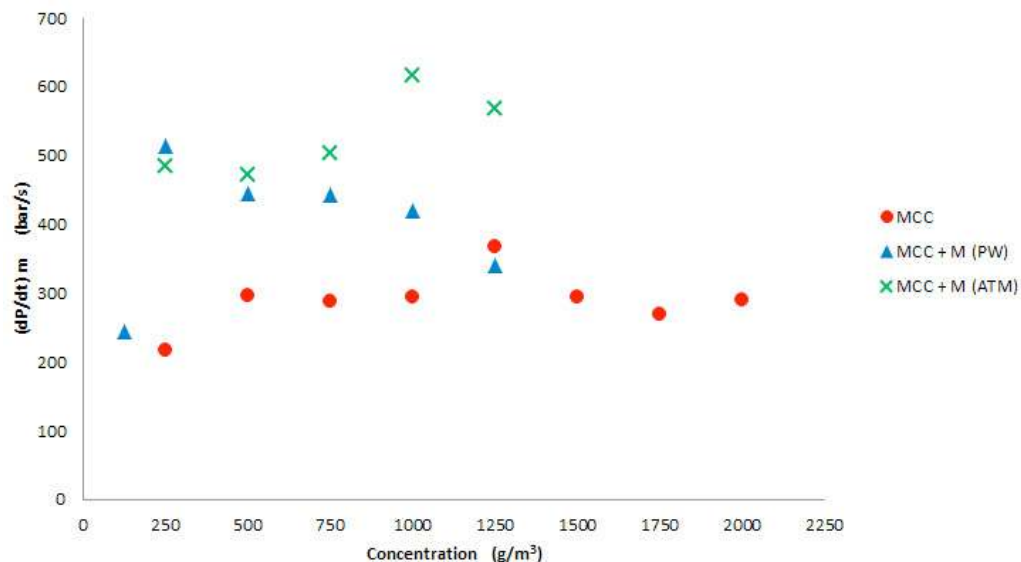
Similarly, Figures 7, 8 and 9 give rate of pressure rise data that further demonstrate the excipient- and admixture-specific nature of the influence of a given solvent. The systems shown are lactose/isopropanol, lactose/methanol and MCC/methanol, respectively.



**Figure 7** Influence of isopropanol admixture on rate of pressure rise of lactose.



**Figure 8** Influence of methanol admixture on rate of pressure rise of lactose.



**Figure 9** Influence of methanol admixture on rate of pressure rise of MCC.

### 3.2 Explosion Likelihood

Tables 5 and 6 give the complete MEC, MIE and MIT data sets for all test conditions. As with  $P_{\max}$  and  $K_{St}$ , the influence of solvent admixture was generally an enhancement of these explosion likelihood (or ignition sensitivity) parameters – i.e., a reduction in MEC, MIE and MIT. Consistent with the pre-wetted lactose  $K_{St}$  values in Table 4, the pre-wetted lactose MIE values are all similar. The effect of inductance via the production of a protracted spark leading to lower MIEs is also seen in Tables 5 and 6.

**Table 5** MEC, MIE and MIT data for MCC.

Material	MEC [g/m <sup>3</sup> ]	MIE [mJ] (Inductance)	MIE [mJ] (No Inductance)	MIT [°C]
MCC	50	30–100 <sup>c</sup> (74) <sup>d</sup>	300–1000 (540)	430
MCC + M (PW)	DL <sup>a</sup>	30–100 (55)	30–100 (67)	380
MCC + E (PW)	DL	10–30 (27)	300–1000 (380)	410
MCC + IPA (PW)	40	30–100 (42)	100–300 (180)	400
MCC + M (ATM)	< 10 (2.6 bar(g)) <sup>b</sup>	ND <sup>e</sup>	ND	ND
MCC + E (ATM)	< 10 (1.5 bar(g))	ND	ND	ND
MCC + IPA (ATM)	< 10 (3.6 bar(g))	ND	ND	ND

<sup>a</sup>DL = Dispersion Limitation. The excipient dissolved in the admixed solvent to the extent that dust dispersion was not possible.

<sup>b</sup>Explosion overpressure at dust concentration of 10 g/m<sup>3</sup>. The explosion criterion is an overpressure of 1 bar(g).

<sup>c</sup>Range of ignition energies from lower value at which no ignition occurred to higher value at which ignition did occur.

<sup>d</sup>E<sub>s</sub> (statistic energy) determined by manufacturer (Kuhner)-supplied software.

<sup>e</sup>ND = Not Determined. The MIKE 3 apparatus used for MIE measurement and the BAM oven used for MIT measurement are not closed systems (unlike the Siwek 20-L chamber used for determination of MEC).

**Table 6** MEC, MIE and MIT data for lactose. (Same footnotes as Table 6.)

Material	MEC [g/m <sup>3</sup> ]	MIE [mJ] (Inductance)	MIE [mJ] (No Inductance)	MIT [°C]
Lactose	70	30–100 (55)	100–300 (250)	420
Lactose + M (PW)	DL	10–30 (17)	100–300 (140)	350
Lactose + E (PW)	DL	10–30 (19)	100–300 (200)	380
Lactose + IPA (PW)	DL	10–30 (14)	100–300 (170)	400
Lactose + M (ATM)	< 10 (4.3 bar(g))	ND	ND	ND
Lactose + E (ATM)	< 10 (2.6 bar(g))	ND	ND	ND
Lactose + IPA (ATM)	< 10 (3.4 bar(g))	ND	ND	ND

#### 4. CONCLUSION

The current work has provided an additional example of how common pharmaceutical solvents such as methanol, ethanol and isopropanol can significantly increase the explosion likelihood and explosion severity of common pharmaceutical excipients such as microcrystalline cellulose and lactose. These explosion enhancement effects have been demonstrated for two modes of solvent admixture – pre-wetting of the excipient powder and direct addition to the combustion atmosphere. The magnitude of the solvent influence on basic explosibility parameters ( $P_{max}$ ,  $K_{St}$ , MEC, MIE and MIT) is dependent on both the nature of the excipient and the method of admixture. Further analysis is underway to facilitate better understanding of the observed phenomena.

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